PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 06 March 2002 (06.03.02)	
Applicant's or agent's file reference 4-31162A/31163	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/09816	**International filing date** (day/month/year) 06 October 2000 (06.10.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
GATLIN, Marjorie, Regan 710 Park Avenue Hoboken, NJ 07030 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
GATLIN, Marjorie, Regan 913 Lovering Avenue Wilmington, DE 19806 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Jean-Luc MARTIN
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF THE RECORDING OF A CHANGE

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Applicant's or agent's file reference 4-31162A/31163	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/09816	**International filing date** (day/month/year) 06 October 2000 (06.10.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
PONGOWSKI, Michele Hammerstrasse 71 CH-4057 Basel Switzerland	US	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
BALL, Michele 9 Shady Lane Kendall Park, NJ 08824 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Jean-Luc MARTIN
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 May 2001 (29.05.01)	
International application No. PCT/EP00/09816	**Applicant's or agent's file reference** 4-31162A/31163
International filing date (day/month/year) 06 October 2000 (06.10.00)	**Priority date** (day/month/year) 08 October 1999 (08.10.99)
Applicant GATLIN, Marjorie, Regan et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 April 2001 (09.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

J. Leitao

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

Date of mailing (day/month/year)
03 octobre 2001 (03.10.01)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
4-31162A/31163

International application No.
PCT/EP00/09816

International filing date (day/month/year)
06 octobre 2000 (06.10.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
NOVARTIS AG
Schwarzwaldallee 215
CH-4058 Basel
Switzerland

State of Nationality: CH
State of Residence: CH
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
NOVARTIS AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

State of Nationality: CH
State of Residence: CH
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer
François BAECHLER

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Form PCT/IB/306 (March 1994)

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(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26639 A2

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(22) International Filing Date: 6 October 2000 (06.10.2000)

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(26) Publication Language: English

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09/415,307	8 October 1999 (08.10.1999)	US
09/415,308	8 October 1999 (08.10.1999)	US

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GATLIN, Marjorie, Regan** [US/US]; 710 Park Avenue, Hoboken, NJ 07030 (US). **PONGOWSKI, Michele** [US/CH]; Hammerstrasse 71, CH-4057 Basel (CH). **DUNNING, Beth** [US/US]; 263 Bradley Street, Battle Creek, MI 49017 (US).

(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/26639 A2

(54) Title: METHOD OF TREATING METABOLIC DISORDERS

(57) Abstract: The invention relates to a combination which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose for simultaneous, separate or sequential use, in particular in the treatment of diseases, especially metabolic disorders; to a method of prevention, delay of progression or treatment of metabolic disorders, more especially diabetes, or a disease or condition associated with diabetes, and to a method of improving the bodily appearance of a warm-blooded animal.

PATENT COOPERATION TREATY

PCT

REC'D 28 FEB 2002

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4-31162A/31163		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09816	06/10/2000	08/10/1999
International Patent Classification (IPC) or national classification and IPC		
A61K31/00		
Applicant		
NOVARTIS AG et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/04/2001	22.02.2002
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hornich, E Telephone No. +49 89 2399 8721

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09816

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-25 as originally filed

Claims, No.:

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3, 5-13 (partly).

because:

☒ the said international application, or the said claims Nos. 8, 9, 12 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3, 5-13 (partly).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-7, 10, 11, 13
	No:	Claims	

2. Citations and explanations
   see separate sheet

SECTION III

1. The IPEA will only formulate an assessment of novelty, inventive step and industrial applicability for the *parts of the present claims for which an International Search Report has been drawn up* (**R. 66.1(e) PCT**)(cf. form PCT/ISA/210, Box I), i.e. only for *those parts relating to the compounds individually structurally identified by name in claims 4 and 5* (repaglinide, acarbose), i.e. ***claims 1-3 and 5-13 partly***.

   It is not obvious which compounds exactly should be encompassed by the definitions '*antidiabetic phenylacetic acid derivative*' (claims 1, 9, 13), '*antidiabetic thiazolidinediones*' as well as '*sulphonyl urea derivatives*' (claim 6), thus the subject-matter of the claims involves unclarity in the sense of **Art. 6 PCT**.

1.1 '*Metabolic disorders*' within claims 9, 10, 11 and 13 does not refer to any particular disease and thus involves unclarity in the sense of **Art. 6 PCT**.

2. Claims 8, 9 and 12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION IV

3. The present application contains *two separate inventions* which are not so linked as to form a *single general inventive concept* (**R. 13.1 PCT**):

   The *problem* underlying the present application is the provision of a combination suitable for the treatment of diabetes.

   The *solution* of the present application resides in the provision of a *combination comprising nateglinide and* ***(a)*** *repaglinide* ('antidiabetic phenylacetic acid derivative') *or* ***(b)*** *acarbose* (for the preparation of medicaments for the treatment of 'metabolic

disorders' (*diabetes*).

The *common linking feature* of *repaglinide* and *acarbose* appears to be the *antidiabetic activity*.

However, combinations of *nateglinide* with other *antidiabetic agents* ('*insulin sensitivity enhancers*'), are already known (see **D2**, p. 9, l. 41-***51***).

Thus, the compounds *repaglinide* and *acarbose* lack any common linking concept. The combinations of each of the two compounds with *nateglinide* thus represent *two separate inventions*.

SECTION V

4. *References*:

D1: PERFETTI R ET AL: 'NOVEL THERAPEUTIC STRATEGIES FOR THE TREATMENT OF TYPE 2 DIABETES' DIABETES/METABOLISM REVIEWS,US,WILEY, NEW YORK, NY, vol. 14, no. 3, 1998, pages 207-225, ISSN: 0742-4221.

D2: EP-A-0 749 751

5. *Novelty* **(Art. 33(2) PCT)** ***with regard to item 1.***

***Neither* D1**, providing *information about different antidiabetic agents* such as for instance repaglinide, nateglinide (both insulin *secretion* enhancers) or acarbose (p. 210, '*Non-Sulfonylurea Insulin Secretagogues*', (*a*) *Repaglinide*; p. 211, (*e*) *A4166*; p. 213, (*a*) *Acarbose*) ***nor* D2**, disclosing pharmaceutical compositions comprising an *insulin sensitivity enhancer* in *combination* with other antidiabetics (e.g. acarbose, nateglinide; see: *abstract*; p. 8, l. 34-39; p. 9, l. 41-*51*: N-[[4-(1-methylethyl)cyclohexyl)carbonyl]-D-phenylalanine = nateglinide), describe *compositions comprising nateglinide and repaglinide or acarbose* (subject-matter of claim 1 *with regard to item 1.*).

Thus, the subject-matter of claims 1-13 could be regarded **nov I.**

6. *Inventive Step* **(Art. 33(3) PCT)** ***with regard to item 1.***

6.1 The *object* of the present application appears to be the provision of a pharmaceutical *composition suitable for 'optimizing and potentially normalizing glycemic control in subjects with type II diabetes'*.

The *solution* of the present application resides in the provision of a *combination comprising nateglinide and (a) repaglinide* ('antidiabetic phenylacetic acid derivative') *or (b) acarbose* (for the preparation of medicaments for the treatment of 'metabolic disorders' (*diabetes*).

6.2 The *antidiabetic effect* of the individual compounds *repaglinide*, *nateglinide* and *acarbose* is known (**D1**); **D1** furthermore teaches that '*combination therapy involving different classes of agents produces synergistic effects in excess ...*' (p. 220, right col., l. 17f.).
Combination therapies in the treatment of diabetes are also known from **D2**, suggesting the combination of *insulin sensitivity enhancers* with e.g. acarbose or nateglinide (see 'novelty').

6.3 Thus, it appears that the present application discloses a(n antidiabetic) combination of compounds, the *antidiabetic properties* of which were already known; combination therapies appear also to be common in the treatment of diabetes, according to **D1** and **D2**.
Furthermore, the experiments described in the present application, involving studies on the effect of nateglinide/repaglinide respectively nateglinide/acarbose combinations on the blood glucose of mice respectively subjects with *type II diabetes* (and not metabolic disorders in general!) do not contain any results showing the difference to combination therapies already known in the art respectively monotherapies. In particular the claimed '*synergistic effect*', occurring under particular conditions (e.g. in a particular amount of the individual components) has not been proved for the individual mixtures with appropriate experimental results.

As the experiments have only been carried out with regard to *diabetes*, the use of the claimed combinations for the preparation of a medicament for the treatment of *metabolic disorders* (claims 11, 13) or *in order to effect a cosmetically beneficial loss of body weight* (claim 12) lack any support by evidence.

6.4 Thus, the mere combination of known compounds (lacking any particular and evidenced effect) which, according to the observations mentioned above, appears to be subject-matter of the present claims 1-13, could ***not be considered support an inventive step.***

7. *Industrial Applicability* **(Art. 33(4) PCT)** ***with regard to item 1.***

7.1 The requirements of industrial applicability appear to be fulfilled for claims 1, 2 and 13.

7.2 For the assessment of the present claims 3-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3, 5-13 (all partially)

Present claims 1-3 and 5-13 relate to compounds defined (inter alia) by reference to the following parameters: " antidiabetic phenylacetic acid derivative", " antidiabetic thiazolidinediones" and " sulphonylurea derivatives".
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.
Consequently, the search has been restricted to those parts relating to the compounds individually structurally identified by name in claims 4 and 5, with due regard to the therapeutic application mentioned in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.